IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Wei ZHANG et al.
International Application No.	:	PCT/EP03/00126
International Filing Date	:	January 9, 2003
U.S. Serial No.	:	10/507,033
For	:	**PROCEDURE AND DEVICE FOR DETERMINING THE HAEMATOCRIT AND/OR BLOOD VOLUME**

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RESPONSE TO MISSING REQUIREMENTS UNDER 35 U.S.C. 371

S I R :

In response to the Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office (DO/EO/US) (mailed April 11, 2005), Applicants submit herewith an English translation of the Specification and Claims, in order to complete the filing requirements for the U.S. national phase of the above-identified PCT application. A copy of the Notification of Missing Requirements is also enclosed.

The Office is authorized to charge the $130.00 processing fee for late filing of the translated Specification and Claims to Deposit Account No. **11-0600.**

The Office is also hereby authorized to charge Deposit Account No. 11-0600 with any additional fees required by this paper or credit any overpayment. An additional copy of this letter is enclosed for this purpose.

Respectfully submitted,
KENYON & KENYON

Date: April 26, 2005

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NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as a Designated / Elected Office (37 CFR 1.495).

- Copy of the International Application filed on 09/07/2004
- Copy of the International Search Report filed on 09/07/2004
- Copy of IPE Report filed on 09/07/2004
- Preliminary Amendments filed on 09/07/2004
- Information Disclosure Statements filed on 09/07/2004
- Oath or Declaration filed on 09/07/2004
- Request for Immediate Examination filed on 09/07/2004
- U.S. Basic National Fees filed on 09/07/2004
- Substitute Specification filed on 09/07/2004
- Priority Documents filed on 09/07/2004

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Translation of the application into English. The current translation of the application into English is defective as described below. Note a processing fee will be required if submitted later than 30 months from the priority date.
  - CLAIMS NOT TRANSLATED
- Processing fee for providing the translation of the application and/or the Annexes later than 30 months from the priority date (37 CFR 1.492(f)).

SUMMARY OF FEES DUE:

Total additional fees required for this application is **$130** for a Large Entity:

- **$130** for English translation surcharge required.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

*A copy of this notice **MUST** be returned with the response.*

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PART 1 - ATTORNEY/APPLICANT COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/507,033	PCT/EP03/00126	2565/123

FORM PCT/DO/EO/905 (371 Formalities Notice)

PROCEDURE AND DEVICE FOR DETERMINING THE HAEMATOCRIT AND/OR BLOOD VOLUME

The invention relates to a method for determining the haematocrit and/or blood volume during an extracorporeal blood treatment with an extracorporeal blood circuit and an apparatus for extracorporeal blood treatment with an extracorporeal blood circuit and a device for determining the haematocrit and/or blood volume.

For the purpose of removing substances usually eliminated with urine and for the purpose of withdrawing fluid, use is made of various methods for machine-aided blood cleaning or blood treatment in acute or chronic kidney failure. Diffusive substance transport predominates in the case of haemodialysis (HD), whilst convective substance transport via the membrane takes place in the case of haemofiltration (HF). Haemodiafiltration (HDF) is a combination of the two methods.

An excessively high or rapid withdrawal of fluid during haemodialysis can give rise to a possibly rapid increase in blood volume, which often leads to an acute drop in blood pressure (hypotony) in the patient.

Hypotony represents one of the main complications in the treatment of blood. There are various solutions to this problem. On the one hand, blood pressure monitors are known which continuously monitor a change in blood pressure and regulate the ultrafiltration depending on the change in blood pressure. On the other hand, blood volume monitors are known which measure the relative blood volume during the dialysis treatment and perform a regulation of the ultrafiltration depending on the relative blood volume.

DE-C-197 46 377 describes a device for the measurement of blood pressure, which is based on the detection of the propagation rate of the pulse waves being propagated via the arterial vessel system of the patient, said pulse waves being generated by the patient's heart contractions. The device permits a continuous, non-invasive measurement of blood pressure, but there is the drawback that the pulse-wave running time is dependent on the haematocrit (HKT).

DE-A-40 24 434 describes a device for the regulation of ultrafiltration, in which the pressure in the extracorporeal circuit is measured in order to determine the relative blood volume. The measured pressure values are stored in chronological sequence and the change in the blood volume is deduced from the! change in the pressure value compared with the value at the start of the treatment. The venous return-flow or

arterial suction-pressure sensor can be used as a pressure sensor. It is pointed out in the publication that the drop in pressure on the arterial cannula is a function of the blood flow and the viscosity of the blood as well as a function both of the diameter and length of the cannula. It is further assumed that the relationship between the blood volume and the change in pressure is linear to a good approximation.

The problem underlying the invention is to provide a method that permits the haematocrit and/or blood volume to be determined with a particularly high degree of accuracy, but with a relatively low technical outlay. Moreover, it is a problem of the invention to provide an apparatus for extracorporeal blood treatment with a device for determining the haematocrit and/or blood volume, which has a relatively simple construction, but a high degree of accuracy.

The solution to this problem tales place according to the invention with the features of claims 1 and 9. Advantageous forms of embodiment are the subject-matter of the sub-claims.

For reasons of safety, the known dialysis devices measure and monitor the arterial pressure $P_{art}(t)$ and the venous pressure $P_{ven}(t)$ in the extracorporeal blood circuit. Moreover, the rate BPR(t) of the blood pump is also measured during the blood treatment, i e. it is known as the control value. The method according to the invention and the apparatus according to the invention make use of the pressure measurement that is already available, so that the outlay on equipment is relatively low.

The basic idea of monitoring the haematocrit and blood volume through the measurement of pressure is based on the following. If the relative blood volume diminishes during the blood treatment as a result of ultrafiltration, the haematocrit in the blood necessarily increases, since the dialysis membrane is not permeable for the blood cells, namely erythrozytes (7.5 Φm), leucozytes (1.5 - 20 Φm) and thromborytes (2.5 Φm). Furthermore, the viscosity increases over-proportionately with increasing haematocrit. Since the flow resistance increases in a markedly linear manner with viscosity, each increase in the haematocrit caused by the reduction in blood volume signifies an increased load on the blood pump, which leads to the fall in the arterial pressure (negative) and the increase in the venous pressure (positive), insofar as the blood pump is operated at the same rate.

It has however been shown that the relationship between blood volume or haematocrit and pressure in the extracorporeal blood circuit is dependent not only on the blood flow, but also on the cannula dimensions, whereby the cannula is to be regarded as the component of the extracorporeal system determining the drop in pressure. The

inventors recognised that the length of the cannula does not have any significant influence on the pressure in the extracorporeal circuit. They recognised that the diameter of the cannula is alone decisive.

In order to increase the accuracy, the respective relationship between haematocrit or blood volume and pressure is stored for different diameters of the cannula and different values of the blood flow in the case of the method and the apparatus according to the invention. The respective data are thus already available before the dialysis treatment. Depending on the respective diameter of the cannula and the value of the blood flow, the respective relationship between haematocrit or blood volume and pressure is then selected and haematocrit and/or blood volume is determined taking account of the selected relationship. The data can for example be stored in the form of groups of curves, which can be described in particular by discrete measurement values.

The increased accuracy results from the fact that account is taken not only of the blood flow during the treatment, but also of the cannula used.

When speaking of haematocrit and blood volume, both absolute values as well as relative values are to be understood, which indicate a relative change in the blood volume in respect of a predetermined initial value, for example the start of the blood treatment.

An evaluation of the clinical data has shown that in practice the arterial pressure, which is measured in the arterial blood line upstream of the blood pump, correlates with the relative blood volume much better than the venous pressure in the venous blood line. This can be traced back to the fact that the venous pressure is very much more susceptible to interference than the arterial pressure. In the case of dialysis machines which make use of balancing chambers, the venous pressure sensor detects pressure fluctuations which are caused not only by the ultrafiltration, but also by switching balancing chambers. The air volume, or more precisely the revel in the venous drip chamber, also has a strong influence on the characteristic of the venous pressure signal. In contrast, the arterial pressure is free from such pressure fluctuations. It is true that the arterial pressure signal is influenced by the blood pumping rate, but here it concerns an unequivocal source of interference whose influence on the arterial pressure can be compensated for.

It has been shown that the cannula diameter can be determined unequivocally by evaluating the pressure changes in the extracorporeal blood circuit. In order to determine the cannula diameter, the change in pressure resulting from a change in the

blood flow is determined and the cannula diameter is deduce from the change in pressure. For this purpose, the pressures are preferably measured at at least two different values of the blood flow in each case, and the difference between the pressures is calculated. In order to determine the cannula diameter, the difference in the pressures is compared with predetermined stored value ranges representative of the individual cannula diameters. The individual value ranges can be assigned unequivocally to the different cannula diameters. The assignment between cannula diameter and value range can in principle be verified again by several measurements.

Furthermore, it has been shown that the relationship between haematocrit or blood volume and pressure for different diameters of the cannula and different values of the blood flow can be described to a sufficient approximation by a non-linear function, for example a second-order polynomial. Since the blood flow correlates with the rate of the blood pump, the pumping rate, which is preset by the control of the blood treatment device, is preferably used to determine the blood flow.

When the haematocrit is determined, the blood volume can be calculated. The blood volume is calculated at a specified time in the blood treatment from the product of the haematocrit at a preceding time and the blood volume at a preceding time divided by the haematocrit at the specified time.

The device for determining the haematocrit and/or blood volume of the apparatus for extracorporeal blood treatment according to the invention has a memory and evaluation unit, in which the respective relationships between haematocrit and blood volume for the different cannula diameters and blood flows are stored. Such a memory and evaluation unit can be part of a computer control, which is already present in the known blood treatment apparatuses. The measurement of the pressure preferably takes place with a pressure sensor which is also already present.

The determination of the cannula diameter on the basis of a pressure measurement is of inherent inventive significance. The knowledge of the influence of the cannula can be used in an advantageous way with the method for blood pressure measurement known from DE-C-197 46 377, in that the influence of the blood density on the pulse-wave running time is compensated for or corrected so that the blood pressure measurement takes place with a higher degree of accuracy.

An example of embodiment of an extracorporeal blood treatment apparatus with a device for determining the haematocrit and/or blood volume as well as an example of embodiment of the method according to the invention are explained below in greater detail with the aid of the figures.

The figures show the following:

Fig. 1 the haematocrit (HKT (%)) as a function of the arterial pressure (P_{art}(mmHg)) for various cannulas of differing diameter and differing length,

Fig. 2 the haematocrit (HKT (%)) as a function of the arterial pressure (P_{art}(mmHg)) for various cannulas,

Fig. 3 the haematocrit (HKT (%)) as a function of the arterial pressure (P_{art}(mmHg)) for various values of the blood flow with a first cannula,

Fig. 4 the haematocrit (HKT (%)) as a function of the arterial pressure (P_{art}(mmHg)) for various values of the blood flow with a second cannula,

Fig. 5 the haematocrit (HKT (%)) as a function of the arterial pressure (P_{art} (mmHg)) for various values of the blood flow with a third cannula,

Fig. 6 an example of embodiment of an extracorporeal blood treatment apparatus with a device for determining the haematocrit and/or blood volume in a simplified diagrammatic representation.

Figure 1 shows the relationship between the haematocrit (HKT (%)) of the blood and the pressure in the arterial blood lime of the extracorporeal circuit with a constant blood pumping rate BPR of 250 ml/min. for seven different dialysis cannulas, which differ from one another in diameter and length. For example, the cannula with the designation V-711 has a diameter of 1.5 mm and a length of 15 mm. The other cannulas are correspondingly designated in figure 1. It can be seen in figure 1 that the relationship between haematocrit and arterial pressure is not linear. It can however be described to a good approximation by a second-order polynomial. Furthermore, it can be seen that the relationship between haematocrit and pressure depends markedly on the diameter of the cannulas. The influence of the length of the cannulas, on the other hand, is relatively small. This can therefore be neglected to a good approximation. For this reason, the relationship is grouped unequivocally according to the diameter of the cannulas, i.e. 1.5, 1.6 and 1. 8 mm. Due to the marked dependence of the relationship on the diameter of cannulas, the measurement of the pressure for the determination of the haematocrit or blood volume without a knowledge of the cannula diameter leads to inaccurate results.

Figure 2 shows the relationship of haematocrit and arterial pressure of a second measurement series with a blood flow rate BPR of 250 ml/min. Here too, the grouping according to the cannula diameters is distinctly marked.

Figure 3 shows the relationship between haematocrit (HKT (%)) and arterial pressure (P_{art} (mmHg)) in the case of a needle with a diameter of 1.8 mm and a length of 20 min for a large number of blood flows BPR between 100 ml/min. and 550 mm/min. Here too, the relationship is not linear. It can however again be described to a good approximation by a second-order polynomial. In a range of blood flow from 160 to 400 ml/min., the curves for different blood flows exhibit a similar gradient. Since the dependence of the blood flow, i.e. the blood pumping rate, is essentially expressed by the fact that the curves are displaced parallel to the x-axis and that the displacement is dependent on the diameter of the needle, the needle diameter can be determined unequivocally. On the assumption that the haematocrit of a dialysis patient lies in the range from 30% to 40%, the diameter of the cannula can be detected without knowledge of the haematocrit. The detection takes place via measurement of the pressure difference with two different blood flows, i.e. blood pumping rates, whereby typical values lie between 130 ml/min. and 310 ml/min.

Figures 4 and 5 show the groups of curves of a needle with a diameter of 1.6 mm and a length of 20 mm and respectively a needle with a diameter of 1.5 mm and length of 15 mm.

The determination of the cannula diameter with the aid of the groups of curves in figures 3 - 5 is explained in greater detail below. Arterial pressures P_{art1} and P_{art2} are measured for this purpose at at least two predetermined blood pumping rates BPR1 and BPR2. The difference $\Delta P_{art} = \Delta P_{art1} - P_{art2}$ is then calculated, which is represented in figures 3 - 5 as a horizontal bar. Values for ΔP_{art} that can unequivocally be assigned to the individual cannula diameters arise for an HKT range of approximately 30 - 40%. These value ranges are previously determined and stored, whereby an appropriate assignment is carried out after measurement of the change in pressure.

The following table shows the pressure difference ΔP_{art}(mmHg) for the three cannulas of differing diameter (1.8, 1.6 and 1.5 min) with a haematocrit HKT of 30 and 40%. The measurement magnitudes can be grouped into the value ranges 70 - 90 mm Hg for a cannula diameter of 1.8 mm, 100 to 120 mm Hg for a cannula diameter of 1.6 min and 130 to 150 mm Hg for a cannula diameter of 1.5 mm. After measurement of pressure difference ΔP_{art}, it can thus be unequivocally decided what diameter the cannula has. It emerges that the haematocrit does not have any influence on the unambiguousness of the detection of the needle diameter when it lies in the physiological range between 30 and 40%.

HKT (%)	ΔP_{art}(mmHg)		
	V-501 (ℓ 1.8 mm)	V-601 (ℓ 1.6 mm)	V-701 (ℓ 1.5 mm)
30	72	102	130
40	89	118	148

Figure 6 shows the essential components of an extracorporeal blood treatment apparatus together with a device for determining the haematocrit and/or blood volume in a simplified diagrammatic representation.

As a blood treatment device, the dialysis apparatus has a dialyser 1, which is divided by a semipermeable membrane 2 into a blood chamber 3 and a dialysis-fluid chamber 4. An arterial blood line 5 leads to the inlet of blood chamber 3, a peristaltic blood pump 6 being connected into said arterial blood line. A venous blood line 7 leads off from blood chamber 3, a drip chamber 8 being connected into said venous blood line. To the ends of the arterial and venous blood line 5, 7 there are connected cannulas 5a, 7a, which are jabbed into the patient. The arterial and venous blood line are a component of a flexible-tube line system designed to be disposable.

Fresh dialysis fluid is prepared in a dialysis-fluid source 9. A dialysis-fluid supply line 10 leads from dialysis-fluid source 9 to an inlet of dialysis-fluid chamber 4 of the dialyser, whilst a dialysis-fluid discharge line 11 leads from the outlet of the dialysis-fluid chamber to a drain 12. The dialysis apparatus also has further components, e.g. a balancing device and an ultrafiltration device etc., which however are not represented for the sake of better clarity. Moreover, the central control unit, which is a component of the dialysis apparatus, is not represented.

For safety reasons, the arterial pressure in arterial blood line 5 is monitored upstream of blood pump 6 and the venous pressure in the venous blood line is monitored downstream of drip chamber 8 in the dialysis apparatus. For this purpose, an arterial pressure sensor 13 is provided in arterial blood line 5 and a venous pressure sensor 14 is provided in venous blood line 7. The device for determining the haematocrit and/or blood volume has arterial pressure sensor 13 already available in the dialysis apparatus as well as a memory and evaluation unit 15. Memory and evaluation unit 15 receives the pressure signal of arterial pressure sensor 13 via a data line 16. Alternatively, the memory and evaluation unit can receive the pressure signal of a venous pressure sensor 14 via a data line 17. Data line 17 is shown by a dashed line in figure 6. Furthermore, memory and evaluation unit 15 is connected to blood pump 6 via a data line 18. A blood pump signal proportional to the blood pumping rate is

transmitted via data line 18. The curve groups represented in figures 3 - 5, which describe the relationship between haematocrit and arterial pressure, are stored in the memory and evaluation unit. The memory and evaluation unit operates as follows.

The cannula diameter, in which the blood pumping rate is varied, is first determined in an initial measurement during the dialysis treatment, whereby the arterial pressures P_{art1} and P_{art2} are measured at two predetermined blood pumping rates BPR of, for example, 310 and 130 mm (figure 3). The memory and evaluation unit calculates from the measured values the amount of the pressure difference $\Delta P_A = P_{art1} - P_{art2}$, which in the present example amounts to 89 mmHg with a haematocrit of 40%. In principle, however, measurements can also be carried out for other haematocrit values, insofar as the haematocrit lies in the physiological range of the patient and thus between 30 and 40%. Apart from the groups of curves, there are stored in the memory and evaluation unit the value ranges from 70 to 90, 100 to 120 and 130 to 150 mmHg characteristic of the cannula diameter, which are described above. The memory and evaluation unit performs an assignment between the measured pressure difference ΔP_{art} and the stored value ranges. Since the measured pressure difference ΔP_{art} lies here in the value range between 70 - 90 mmHg, the memory and evaluation unit assumes that the cannula has a diameter of 1.8 mm (figure 3).

After the cannula diameter has been ascertained in the initial measurement, the memory and evaluation unit carries out a selection between the different curve groups (figures 3 - 5), which respectively describe the relationship of haematocrit and arterial pressure for the respective needle diameter. The memory and evaluation unit selects here the group of curves according to figure 3, which are representative of the present needle diameter of 1.8 mm.

After the selection of the appropriate curve group, the memory and evaluation unit determines from the appropriate curve group, with a high degree of accuracy, the appropriate haematocrit in dependence on the blood pumping rate BPR(t) taking account of the diameter of the employed cannula, without the diameter of the used cannula needing to be inputted manually. If, for example, an arterial pressure of 100 mmHg is measured with the arterial pressure sensor, a haematocrit of approx. 33% results with a blood pumping rate of 310 mm (fig. 3). With decreasing blood pumping rate, the haematocrit increases according to the curve group.

The determination of the blood volume takes place after the haematocrit has been ascertained. The blood volume at a specified time in the blood treatment RBV(t) is calculated from the haematocrit HKT according to the following equation:

$$RBV(t) = \frac{HKT(t_o)RBV(t_0)}{HKT(t)}$$

whereby RBV(t) is the blood volume at time t,
HKT(t) is the haematocrit at time t and RBV (t_o) and HKT (t_0) are respectively the blood volume and the haematocrit at an arbitrary time t_o, which lies before time t.

Since RBV (t_o) = 1 at the start of the dialysis treatment, the memory and evaluation unit can determine RBV(t) relative to this time. On the other hand, the above equation can also be used for two arbitrary times t_0 and t if t_0 does not coincide with the start of the treatment and RBV (t_o) is thus not necessarily 1. If RBV (t_o) is not known, the memory and evaluation unit can however determine relative changes in RBV according to the above equation compared with a value of RBV (t_o) of 1.